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INSIDE

More Bad News for Folic Acid

ABSTRACT & COMMENTARY

ELEVATED HOMOCYSTEINE LEVELS HAVE BEEN ASSOCIATED with atherosclerosis. Folic acid supplementation is a simple inexpensive way to reduce homocysteine levels, which has become popular for secondary prevention in patients with coronary artery disease (CAD), despite a paucity of long-term clinical trial data. Thus, Liem and colleagues from the Netherlands studied 593 patients with stable CAD on statins who were randomized to open-label folic acid 0.5 mg/d or standard care, which included aggressive pursuit of lipid goals. The primary end point was a composite of death and major vascular events over 24 months. In folic acid-treated patients homocysteine levels decreased 18% from 12 to 9 mmol/L but didn't change in the control group ($P < .001$). The primary end point was 10% in the folic acid group and the control group (relative risk, 1.05). In a subgroup where it was measured, C-reactive protein levels were unchanged in both groups. Liem et al concluded that over 2 years, folic acid supplementation in stable CAD patients on statins, despite reducing homocysteine levels, does not reduce clinical vascular events or death and that its use should not be encouraged (Liem A, et al. *J Am Coll Cardiol.* 2003;41:2105-2113).

COMMENT BY MICHAEL H. CRAWFORD, MD

This study, following on the heals of the recent negative trial in postpercutaneous coronary stenting patients, suggests that we have more to learn about the role of folic acid and homocysteine in CAD. Explanations for the negative results include that in patients on maximum doses of statins at target lipid levels, there may be little to gain with vitamin therapy. Also, some believe that homocysteine is a marker for more diffuse vascular disease and lowering it does little because it is not causative. Support for this latter explanation comes from this study and others, which have noted that homocysteine levels are related to creatinine clearance. Reduced renal function due to vascular disease is a poor prognostic sign and indicates diffuse vascular disease. Thus, homocysteine levels may correlate with the risk of vascular events, but lowering it may not reduce their incidence.

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There are several weaknesses of this study that diminish its authority and make us hold off on definitive conclusions until some of the larger, longer trials are completed (NORVIT, VITATOPS, SEARCH). First, based upon previous observational studies in established CAD patients, it was powered for a larger difference in events than has been observed in trials of patients without preexisting vascular disease. Consequently, it may have been underpowered to detect small differences (ie, 15%) in events. Second, the duration of therapy was short (24 months) and the number of patients was relatively small (fewer than 600). Third, about 15% of patients in both groups were already on B vitamin supplementation, which was not discontinued. Finally, the dose of folic acid in this study was low (0.5 mg/d) compared to other studies in which megadoses have been used (5 mg/d). On the other hand, significant reductions in homocysteine levels were observed with this dosage. Interestingly, the Netherlands, where this study was done, does not fortify grain products with folic acid as is done in other industrialized nations. Therefore, lower doses of folic acid may have a more profound effect in this environment. Regardless, Liem et al's admonition that the routine use of folic acid supplementation should be tempered until more trial outcomes are available seems reasonable given the latest study results. ■

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Interferon-Beta for Viral Myocarditis

ABSTRACT & COMMENTARY

Synopsis: *INFB therapy of heart failure patients with persistent viral genomes in the myocardium was safe, eliminated viral genomes, and improved LV function.*

Source: Kühl U, et al. *Circulation*. 2003;107: 2793-2798.

PATIENTS WITH PERSISTENT HEART FAILURE DESPITE therapy and myocardial biopsy evidence of virus genomes have a poor prognosis. Thus, Kühl and associates from Berlin, Germany, studied 22 patients who met these criteria and had enteroviral (65%) or adenoviral (35%) genomes detected by polymerase chain reaction analysis of myocardial biopsy material. All had persistent heart failure symptoms for a mean of 44 months, and average left ventricular (LV) ejection fraction (EF) was 45%. Interferon-beta (INFB) was given subcutaneously 3 times a week for 24 weeks. Therapy was well tolerated, and no patient deteriorated. Repeat endomyocardial biopsy showed clearance of viral genomes in all of the patients. LV volumes decreased significantly, and EF increased to 53% ($P <$ .001). LVEF normalized in 9 patients and increased > 5% in 5. These 14 patients had mild-to-moderate LV dysfunction. Those with severely impaired LV function were less likely to improve. New York Heart Association class improved in two-thirds of the patients. Biopsy results after treatment showed a decrease in CD3-positive T lymphocytes, but there was no evidence of active myocarditis on either the pre- or postspecimens. Kühl et al concluded that INFB therapy of heart failure patients with persistent viral genomes in the myocardium was safe, eliminated viral genomes, and improved LV function.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Current supportive heart failure therapy has reduced morbidity and mortality, but adverse outcomes are still frequent. Clearly, an approach based upon eliminating the cause of myocardial dysfunction would be advantageous. This study is an attempt to pursue this line of therapy for viral myocarditis using the antiviral agent INFB. Several lines of evidence from previous studies support their approach. First, the detection of viral genomes in myocardial biopsy specimens is correlated with a worse prognosis. Second, immunosuppressive therapy often fails when viral genomes are detected. Third, lack of evidence of an inflammatory response in

the myocardium correlates with the presence of viral genomes and a poor prognosis. Thus, in this pilot study of highly selected patients with persistent LV dysfunction, so spontaneous remission is not likely; patients with persistence of viral genomes on myocardial biopsy; and patients with little or no evidence of an inflammatory myocarditis, INFB therapy was generally beneficial, and no treated patient deteriorated over 6 months.

This study is remarkable for the long duration of cardiomyopathy (mean duration, 44 months) in the patients. However, most of the patients had relatively preserved LV function (mean EF, 45%) and those with more marked LV dysfunction did not improve. Thus, such therapy must be given before irreversible myocardial damage occurs, which may not always be feasible. This will be the real challenge for this approach—identifying patients early who will respond to antiviral therapy. Previous studies of the value of myocardial biopsy were not encouraging because they focused on evidence of myocarditis, which was uncommonly found. This focus on viral genome presence, if it pans out, may resurrect the myocardial biopsy. Because of the encouraging results of this pilot study, a large, randomized trial has begun. We will eagerly await the results, but in the mean time, there may be hope for some patients with viral myocardiopathy, even if they have persistent LV dysfunction for years. ■

Natriuretic Peptide Levels in Mitral Regurgitation

ABSTRACT & COMMENTARY

Synopsis: *Plasma natriuretic peptides are related to the severity of mitral regurgitation and the presence of symptoms but not LV size or function.*

Source: Sutton TM, et al. *J Am Coll Cardiol*. 2003; 41:2280-2287.

Decisions regarding appropriate therapy in patients with mitral regurgitation depend on an accurate assessment of the severity of regurgitation. Although echocardiograpy is the preferred method for making this determination, it is a technically demanding challenge without generally agreed upon criteria. Thus, another complementary approach would be welcomed to this endeavor. Accordingly, Sutton and colleagues from New Zealand explored the concept that natriuretic peptide levels (ANP, BNP) may aide in the determination of the severity of mitral regurgitation. They selected 49 patients with isolated mitral regurgitation and left ventricular ejection fraction (LVEF) > 55% for the study. All patients had a complete echocardiographic assessment and 3 natriuretic peptide levels measured. They also studied 100 normal controls. The majority of patients had mitral valve prolapse (33) but 15 had rheumatic disease, 4 of whom had mild mitral stenosis (valve area < 1.5 cm^2). Symptoms were present in 33 patients, and 16 were asymptomatic. Symptomatic patients more often had atrial fibrillation, more severe regurgitation, and larger left atria. Other characteristics including LV size and EF were not different in symptomatic patients. Natriuretic peptide levels rose with increasing severity of regurgitation and left atrial size but were unrelated to LV size and function. Symptomatic patients had higher natriuretic peptide levels as compared to asymptomatic patients (BNP 17 vs 7 pmol/L, $P < .001$), and asymptomatic patients had higher levels than controls (BNP 5 pmol/L, $P < .0001$). Accuracy for predicting symptoms was .89-. 90 (area under the receiver operating curve) for the natriuretc peptides, .88 for the mitral regurgitation index,[1] .81 for left atrial size, and .63 for LV size. Sutton et al concluded that plasma natriuretic peptides are related to the severity of mitral regurgitation and the presence of symptoms but not LV size or function.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

There are 2 major frustrations in the evaluation of patients with mitral regurgitation. By far, the greatest is determining the severity by echocardiography. Since there is no one measurement technique that all agree is adequate for this purpose, some labs use combinations of findings or one of the published indexes, but most labs just use a qualitative visual assessment for which there are no universally agreed criteria. Hence one reader's mild is another's moderate regurgitation. Some stick to mild, moderate, and severe, and other labs use a 6-point differentiation system. This unsatisfactory situation begs for another technique to determine the severity of mitral regurgitation. Are natriuretic peptides the answer? Probably not. In this study, they were related to regurgitation severity and symptoms in general, but they are unlikely to be precise enough in an individual patient for clinical decision-making. In fact, the limited clinical follow-up information provided in this paper confirms this limitation: One asymptomatic patient who developed worsening LV function and symptoms and was referred for surgery had a BNP level of 4 pmol/L.

The other problem with evaluating patients with mitral regurgitation is determining if they have symptoms related to the valve lesion, since such symptoms as dyspnea and fatigue are nonspecific. Will natriuretic peptide levels help in this assessment? Perhaps. In this study, there was a clear relationship to symptoms, and all the patients with symptoms referred for surgery had elevated levels of BNP

(11-52 pmol/L). The real question is whether natriuretic peptide levels will be of value for following asymptomatic patients to determine the timing of operation. This study was not designed to answer that question, but it does support the concept enough that perhaps a trial is in order.

There are limitations to the use of natriuretic peptides for these purposes that must be addressed. Natriuretic peptides increase with age, are higher in women than in men, and are inversely related to body surface area. Obviously these factors need to be taken into consideration and currently there is no easy way to do this. Also, the value of natriuretic peptides in patients with enlarged LVs or reduced LV function and mitral regurgitation is unclear since such patients were excluded from this study. It would be expected that these findings would raise natriuretic peptide levels regardless of mitral regurgitation, but more information is needed in this regard. Of interest in this study was the finding that natriuretic peptides were related to left atrial size. Previous studies have shown that left atrial enlargement is a poor prognostic sign in chronic mitral regurgitation, perhaps because it foreshadows the development of atrial fibrillation. This relationship may be another strength of measuring natriuretic peptides in mitral regurgitation patients. In summary, measuring natriuretic peptides in mitral regurgitation patients may be of value for discerning significant symptoms from nonspecific ones and may contribute to the determination that severe mitral regurgitation exists, but the limitations of this one measurement need to be taken into consideration. ■

Reference

1. Thomas L, et al. *J Am Coll Cardiol*. 1999;33:2016-2022.

Adverse Effect of Ventricular Pacing on Heart Failure and Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *Right ventricular apical pacing contributes to heart failure hospitalization and atrial fibrillation in patients with sinus node dysfunction. Ventricular desynchronization caused by right ventricular pacing is responsible for this phenomenon.*

Source: Sweeney MO, et al. For the MOde Selection Trial Investigators. *Circulation*. 2003;107:2932-2937.

Sweeney and colleagues from the MODE Selection Trial (MOST) report on the effects of ventricular pacing in patients with sinus node dysfunction. MOST is a prospective randomized comparison of single-chamber ventricular rate modulated pacing (VVIR) vs dual-chamber rate modulation pacing (DDDR) in patients with sinus node dysfunction. In both groups, the lower rate limit was programmed to at least 60 bpm with an upper rate limit of at least 110 bpm. In the DDDR group, the programmed AV delay was suggested to be between 120 and 220 msec. The primary end point was mortality, and an earlier report had shown no difference between the groups. The frequency of heart failure hospitalizations and the documented occurrence of atrial fibrillation were secondary end points used in the study. At each follow-up clinic visit, the mean percent of ventricularly paced beats over all visits was calculated. A similar calculation was done for atrial pacing in the DDDR group. In MOST, the average age was 73, and there were equal numbers of males and females. The mean left ventricular ejection fraction was 55%, and most patients had mild or no symptoms of congestive heart failure at baseline. Prior atrial arrhythmias had been noted in 54% of the patients. The median cumulative percent of ventricular pacing was significantly higher in the DDDR group vs the VVIR group (90% vs 58%; $P = .001$). Approximately half of the patients in the DDDR group were ventricularly paced either continuously or near continuously (greater than 90% of the time) compared with only 20% in the VVIR group. There were 1339 patients in MOST who had a baseline QRS duration of less than 120 msec. The influence of cumulative percent of ventricular pacing on heart failure hospitalization was analyzed in this subgroup.

The overall rate of heart failure hospitalization in the 2 pacing modes was similar (10% DDDR, 9% VVIR). However, in the DDDR mode, the risk of heart failure hospitalization increased as the percentage of ventricular pacing increased. Ventricular pacing greater than 40% of the time in the DDDR mode was associated with a 2.6-fold increased risk of an increase in heart failure class compared with pacing less than 40% of the time. The slope of increasing risk was relatively flat above 40% paced beats. In the VVIR mode, the risk was level between 0% and 80% ventricular pacing, with a sharp increase in heart failure risk in those paced more than 80% of the time. When the influence of ventricular pacing on the risk for heart failure hospitalization was adjusted for a history of prior heart failure, the ejection fraction, and use of antiarrhythmic therapy, the hazard ratio was lower but still significant.

A similar analysis was performed for development of atrial fibrillation. The risk for developing atrial fibrillation increased in both pacing modes in parallel with

increases in the cumulative percent of ventricular pacing. The overall rate of atrial fibrillation was slightly higher in the VVIR group (24%) vs the DDDR group (21%). There was an increasing risk for atrial fibrillation from 0% up to about 80% or 85% ventricular pacing in both pacing modes. A life-table analysis showed that the risk for atrial fibrillation occurred early in the VVIR mode and somewhat later in the DDDR group.

Sweeney et al conclude that right ventricular apical pacing contributes to heart failure hospitalization and atrial fibrillation in patients with sinus node dysfunction. They postulate that ventricular desynchronization caused by right ventricular pacing is responsible for this phenomenon.

COMMENT BY JOHN DiMARCO, MD, PhD

When first introduced, dual-chamber pacing was meant to represent a more physiologic form of pacing than single-chamber ventricular pacing. Current guidelines recommend dual-chamber or atrial pacing in patients with sinus node dysfunction. In the United States, dual-chamber pacing is more commonly used than atrial pacing with a single-chamber device. In controlled clinical trials, however, it has been difficult to show that dual-chamber pacing is superior to single-chamber ventricular pacing in patients with sinus node dysfunction. In contrast, AAI(R) pacing has been shown to be superior to VVI(R) pacing in these patients in well-controlled studies. The observation that right ventricular apical pacing induces ventricular dyssynchrony is an explanation for these observations. This study from a trial looking at DDDR vs VVIR pacing in patients with sinus node dysfunction offers further insights. The risk of heart failure hospitalization and atrial fibrillation are related to the proportion of right ventricularly paced beats. This observation was made even though this patient group had a low baseline incidence of symptomatic heart failure and systolic dysfunction.

There are ways to minimize the negative hemodynamic effects of right ventricular pacing. Certainly, single-chamber atrial pacing would be effective. If patients with abnormal AV conduction are excluded at baseline, the risk of progression to heart block is low and atrial pacing should be the preferred mode. If there is some risk of AV block, new pacing algorithms available in some models allow adaptations in the AV interval that allow normal AV conduction to occur without risking prolonged first-degree or higher-grade AV block.

Another solution to the problem of dyssynchrony caused by right ventricular pacing is the use of biventricular pacing. However, biventricular pacing devices require a more complicated implant procedure, and late problems with the left ventricular pacing lead are common. Therefore, biventricular pacing should still be reserved for patients who need ventricular pacing and are likely to develop heart failure with right ventricular pacing alone. ■

Temporal Trends in Sudden Cardiac Arrest

ABSTRACT & COMMENTARY

Synopsis: *The static temporal pattern of overall survival in EMS-treated out-of-hospital cardiac arrest is the result of a balance between improved EMS services and several patient factors associated with decreased probability of survival.*

Source: Rea TD, et al. *Circulation*. 2003;107: 2780-2785.

Rea and colleagues report a longitudinal survey of cardiac arrests in King County, Wash, (excluding the city of Seattle) from 1977 to 2001. The year 1977 was the year in which paramedic services were introduced in this area. The study area has a 2-tiered emergency medical services (EMS) response system. Fire engines and/or basic life support (BLS) units staffed by regular fireman provide the first tier. Paramedic-staffed advanced life support (ALS) units provide the second tier. BLS defibrillation was introduced in the late 1970s and became operational throughout the county by 1986. A program of dispatcher-assisted telephone bystander cardiopulmonary resuscitation (CPR) was initiated in 1982.

During the entire study period, the EMS treated 12,591 persons with out-of-hospital cardiac arrests. Of these, 4775 persons had witnessed ventricular fibrillation caused by heart disease. The average age, the intervals for BLS and ALS response, and the proportions who were women, were treated with citizen CPR, were defibrillated by BLS, and had arrested before EMS arrival all increased over time. The average defibrillation response interval and the proportions who were witnessed and who presented in ventricular fibrillation decreased over the study period. There was a decrease in the proportion of patients with cardiac arrest in private residences and an increase in the proportion of cardiac arrests in either nursing homes or nonhospital medical facilities. Several factors were associated with the probability of survival. For the group of patients with wit-

nessed ventricular fibrillation, increasing age, arrest before EMS arrival, and longer intervals for BLS, ALS, and defibrillation were all associated with decreased survival. Location of the arrest in a public place and bystander CPR were associated with improved survival. When patients with all rhythms at time of cardiac arrest were analyzed, female gender, arrest in a nursing home, and arrest before arrival were strongly associated with a poor outcome. Survival was improved for a witnessed arrest, for an arrest in a public place, and when the presenting rhythm was ventricular fibrillation. Rea et al constructed several models that adjusted for changes in the overall EMS system and in the clinical characteristics such as age, gender, and location that were independent of the EMS system. Overall survival for witnessed ventricular fibrillation improved somewhat from 1977 to 1981 to 34.4% in 1986-1989 but since then has remained relatively flat. For all cardiac arrests, the crude survival rate has actually decreased. Between 1977 and 1981, 17.5% of cardiac arrest victims survived, but during the period of 1998 to 2001 survival was only 15.7%. The decrease in survival was accounted for by changes in age, gender, witness status, the presenting rhythm, and the frequency of arrest before EMS arrival.

Rea et al conclude that the static temporal pattern of overall survival in EMS-treated out-of-hospital cardiac arrest is the result of a balance between improved EMS services and several patient factors associated with decreased probability of survival. The latter factors are beyond EMS control and may represent overall population trends. Although improvements in EMS services through more widespread availability of public access defibrillation, changes in CPR, and communication may enhance survival in selected individuals, the overall mortality may change little.

COMMENT BY JOHN DiMARCO, MD, PhD

This longitudinal study from a region with perhaps the best emergency medical system in the country adds important data. As treatments for coronary artery disease and heart failure have improved, those suffering an out-of-hospital cardiac arrest are likely to be older, of female gender, and in a nursing home or nonhospital medical facility. As a result, a larger proportion of cardiac arrest victims are now found to be in rhythms other than ventricular fibrillation. These rhythms, which include asystole and pulseless electrical activity, are associated with a much worse prognosis since they usually cannot be reversed simply by electrical defibrillation. Although in some settings, like casinos and airports, survival to hospital discharge is excellent, these patients do not typify the average cardiac arrest victim.

The changes in the demographics of sudden cardiac death demonstrates the triumph of cardiovascular medicine in that we can now delay or postpone progression of cardiovascular disease. However, this raises new problems as the typical cardiac arrest victim is now older and more likely to have severe underlying cardiac and noncardiac disease. Devoting increased resources to try to improve survival further in locales like Kings County, Wash, where mature EMS systems are already in place, may not prove cost-effective. Rather, low-cost innovations that can target improving outcome in the decreasing number of highly salvageable patients seem most promising. ■

A Prevention Cocktail for Diabetics: The Emerging Role of Statins

ABSTRACT & COMMENTARY

Synopsis: *HPS provides definitive evidence that . . . statin therapy can produce substantial reductions in the risk of heart attacks, strokes, and revascularization in diabetics, even if there is diagnosed coronary or other vascular disease.*

Source: Collins R, et al. For the Heart Protection Study Collaborative Group. *Lancet*. 2003;361: 2005-2016.

OVER A YEAR AGO THE HEART PROTECTION STUDY (HPS) investigating the efficacy of simvastatin (simva) and antioxidant vitamins was published.[1] An across-the-board, robust reduction in vascular events was seen in the simva cohort in this huge trial of 21,000 individuals who had vascular disease or were at high risk by nature of having diabetes or treated hypertension. The HPS results were particularly tantalizing in that they demonstrated comparable relative risk reduction in individuals who had baseline normal and below normal total and LDL cholesterol values, as well as in diabetics of whom 50% had no clinical vascular disease. The present report is a detailed analysis of the approximate 6000 diabetics in HPS; of this cohort, 33% had a history of coronary artery disease (CAD), 18% had "other occlusive arterial disease," and 49% had no history of arterial disease. Ninty percent were type II diabetics, and 10% were type I. Compared to nondiabetics, the diabetic cohort was slightly younger and had somewhat less men (who represented over 70% of the group); there were no sig-

nificant differences in lipid levels between groups. Subjects from general practice clinics who met entry criteria were randomized to simva 40 mg daily or placebo. Mean follow-up was 4.8 years for diabetics and 5.0 years for all remaining subjects. Diabetics represented approximately 29% of the entire HPS cohort.

The results in the diabetic cohort were essentially identical to the larger group. There was an approximate 27% reduction in the primary end point of coronary death or nonfatal myocardial infarction ($P < .0001$), as well as a comparable reduction in all major coronary events. Diabetic CAD mortality was 8.0% placebo vs 6.5% simva ($P = .02$) and for first nonfatal MI, 5.5% vs 3.5% ($P = .0002$). There was a 25% reduction in stroke in both the diabetic and nondiabetic cohorts. There was a 17% reduction in coronary revascularization in diabetic subjects compared to 24% in the entire HPS cohort, but this difference was not significant. Diabetics on simva had a slightly lower incidence of peripheral vascular disease complications, and renal function impairment was somewhat slowed by the statin. Of great interest, in the 50% of diabetics who did not have a diagnosis of vascular disease at entry, there was a 33% reduction in first major vascular event (9.3% vs 15.5%; $P = .003$), with an overall 25% reduction for the entire diabetic cohort, regardless of age or gender.

Individuals with a variety of baseline lipid abnormalities had no difference in the relative risk reduction of 27%, including those whose initial LDL cholesterol was < 116 mg/dL. A total of 1343 diabetics had a pretreatment LDL cholesterol of < 116 mg/dL; these achieved a 30% reduction in first major vascular events, 8% vs 11% ($P = .05$). The placebo group in the entire HPS cohort had a 5% per year risk of a major vascular event over the 5-year follow-up; simvastatin reduced this risk by approximately 25%. As in the original publication, the investigators argue that the rates of significant drop-in statin use in the placebo group of 17%, as well as a 15% drop-out rate in the simva cohort, suggest that the actual risk reduction with simvastatin vs no lipid therapy would approach one-third rather than one-fourth. There was no difference in the onset of new diabetes, and there were no effects on diabetic control. The authors conclude that "HPS provides definitive evidence that . . . statin therapy can produce substantial reductions in the risk of heart attacks, strokes, and revascularization in diabetics, even if there is diagnosed coronary or other vascular disease."

The reduction of LDL cholesterol with simva was approximately 1.0 mmol/L (39 mg/dL) and was achieved in both diabetics and nondiabetics. In HPS diabetics who began with an LDL cholesterol of < 116 mg/dL, the LDL levels were lowered to < 77 mg/dL; this was accompanied by a 25% reduction of macrovascular disease, comparable to the relative risk reduction in those individuals with higher baseline cholesterol. HPS investigators stress that vascular risk should drive statin therapy as determined by a diagnosis of occlusive arterial disease or diabetes, rather than baseline lipid levels. In fact, LDL cholesterol in HPS was relatively unremarkable at baseline. Diabetics who had vascular disease at entry had a 3-fold greater likelihood of having a major vascular event, although the relative risk reduction was similar. Of interest, not only was the first event reduced by statin therapy, but subsequent events during the 5-year trial also were decreased. They concluded, "HPS has shown that the benefits of cholesterol-lowering statin therapy are additional to those of other cardioprotective treatments. In particular, statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of such major vascular events, irrespective of their initial cholesterol concentration."

COMMENT BY JONATHAN ABRAMS, MD

The results in the diabetic cohort in HPS speaks for itself. This is an extremely large cohort, far larger than all of the diabetic patients combined in prior statin trials. While the NCEP-ATPIII and American Diabetes Association have already established diabetes as a coronary risk equivalent, with a target LDL cholesterol of 100 mg/dL, it is noteworthy that many to most type II diabetics do not have a significant LDL abnormality and actually have comparable LDL levels to the general population. Statins are less effective for the high-triglyceride/low-HDL abnormality of diabetics.

Of interest, another study of statin therapy in diabetics from the United Kingdom and Ireland (CARDS) has just been prematurely terminated because of a highly significant reduction in the primary end point of multiple major vascular events ($P = .005$). In CARDS, 2800 patients were randomized to placebo or atorvastatin 10 mg. These were type II diabetics with at least one major risk factor for CAD, but who had no overt vascular disease at entry and would not otherwise qualify for lipid-lowering therapy according to UK guidelines. Specific data is not yet available. On the other hand, recent satin results from ALLHAT and ASCOT were somewhat disappointing in the diabetic cohorts. A narrow LDL differential between active statin therapy and placebo during these trials rendered the results less conclusive than HPS, particularly in diabetics.

In conclusion, it seems incontrovertible that a statin should be prescribed for diabetics who are at high risk. These include those with one or more major CAD risk factors, older individuals, and all diabetics with overt

vascular disease, be it peripheral, cerebrovascular, or coronary. Half of the diabetics in HPS had no vascular disease at entry and an unknown frequency of the major risk factors; the mean age in HPS in the diabetics was 62. These data suggest that any middle-aged type II diabetic should receive a statin, even if the LDL cholesterol is close to 100 mg/dL or lower. The premature cessation of CARDS and the HPS data suggest that it does not matter which statin is used, so long as a clinically effective dose is chosen. Diabetics without overt vascular disease have a roughly comparable risk to nondiabetics with documented CAD; one should be able to extrapolate HPS and CARDS data to any adult type II diabetic. HOPE supports the use of an ACE inhibitor in diabetics older than 55 with an additional risk factor, and other data, although less conclusive, indicates that aspirin is protective in these patients. Current guidelines support aggressive blood pressure control in diabetics, with a target of < 120/80 mm Hg. Thus, a preventive cocktail for the type II diabetic should include aspirin, an ACE inhibitor, a statin, and usually 2 or more drugs for hypertensive therapy in those with elevated blood pressure. Glycemic control is deemed to be most important, but data are lacking supporting a significant macrovascular event differential between low vs high HgbAIC. It may well be that greater vascular protection is provided by a generic prevention cocktail than optimal fine-tuning of blood sugar in type II subjects.

Addendum

The HPS had a 4 × 4 factorial design and also examined an antioxidant combination compared to placebo. That part of the study was negative. In the same issue of *Lancet*[2] as the diabetic HPS report, a meta-analysis of antioxidant vitamins for the prevention of cardiac disease concluded that there is no data supporting use of these agents. ■

References

1. *Lancet*. 2002;360:7-22.
2. *Lancet*. 2003;361:2017-2023.

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7. Diabetic patients should receive which of the following therapy to prevent cardiovascular events?
a. A statin
b. Aspirin
c. ACE inhibitor
d. All of the above

8. The risk of heart failure and atrial fibrillation in patients with a pacemaker for sinus node dysfunction is related to:
a. lack of a rate responsive function.
b. the lower heart rate limit.
c. the percent time of right ventricular pacing.
d. VVIR rather than DDDR pacing.

9. The lack of improvement in out-of-hospital resuscitation rates by EMS personnel is related to:
a. improvements in EMS services.
b. adverse characteristics of the cardiac arrest population now.
c. fear of contracting AIDS.
d. a and b

10. Antiviral therapy for suspected viral myocarditis is contraindicated when:
a. viral genomes are absent on biopsy.
b. LV dysfunction has been present for > 2 years.
c. there is no evidence of inflammation on biopsy.
d. heart failure is mild.

11. Clinical trial data clearly supports which of the following for secondary prevention in CAD?
a. Aspirin
b. Folic acid
c. Vitamin E
d. Fish oil

12. Natriuretic peptide plasma levels in patients with mitral regurgitation are related to:
a. the severity of regurgitation.
b. symptoms.
c. left atrial size.
d. All of the above

Answers: 7(d); 8(c); 9(d); 10(a); 11(a); 12(d)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Cardiology Alert*. Send your questions to: Christie Messina, *Clinical Cardiology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Cardiology Alert* via the internet by sending e-mail to christie.messina@ahcpub.com. We look forward to hearing from you. ■